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HEART RATE AND BLOOD PRESSURE RESPONSES TO INTRAVENOUS BOLUSES OF ISOPRENALINE IN THE PRESENCE OF PROPRANOLOL, PRACTOLOL AND ATROPINE

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1 Six healthy subjects were studied on two occasions. Graded bolus injections of isoprenaline sulphate were given intravenously and control dose-response curves were drawn for the changes in heart rate and blood pressure. In a random order each subject received an intravenous infusion of either propranolol or practolol and further dose-response curves were constructed PRE- and POST-atropine (0.04 mg/kg).

2 Exercise tachycardia was reduced 26.1 ± 2.7% by propranolol and this was not significantly different from the reduction by practolol (21.2 ± 1.9%).

3 Propranolol attenuated the isoprenaline tachycardia (dose ratio 43.7) and after atropinisation the dose ratio was not significantly altered (41.1). Practolol also attenuated the isoprenaline tachycardia (dose ratio 4.4) but after atropinisation the dose ratio was significantly increased to 8.8, though this remained significantly less than the dose ratio for propranolol.

4 At a heart rate increase of 25 beats/min, the isoprenaline-induced control fall in mean blood pressure was 9–11 mm Hg. After propranolol administration this fall was converted to a small increase of +2.3 ± 1.3 mm Hg. Following practolol, however, the mean blood pressure reduction was 19.7 ± 2.9 mm Hg. Practolol did not significantly block the isoprenaline-induced fall in diastolic pressure.

5 The difference in potency of propranolol and practolol, demonstrated by their effect on isoprenaline induced tachycardia at doses shown to have equal effects on exercise tachycardia, is contributed to but not fully explained by the reflex withdrawal of cardiac vagal tone which occurs with cardioselective but not non-selective antagonists.

Keywords i.v. isoprenaline bolus propranolol practolol atropine heart rate blood pressure

Introduction

The comparative potency of cardioselective and non-selective β-adrenoceptor antagonists appears to differ according to the method of assessment used. Thus at doses adjudged equipotent by their effect on exercise tachycardia, cardioselective antagonists will be less effective than non-selective β-adrenoceptor blocking drugs in inhibiting an isoprenaline tachycardia (De Palen *et al.*, 1976; Perucca *et al.*, 1981). It has been suggested that the tachycardia induced by isoprenaline is made up of two components—direct sino-atrial stimulation and reflex vagal withdrawal following an isoprenaline-mediated fall in blood pressure (Dunlop & Shanks, 1968)—and that this could explain the observed differences between the drugs (Brick *et al.*, 1968). Cardioselective antagonists, by not blocking peripheral β_2-receptors, would allow a fall in blood pressure to occur and a reflex vagal component to heart rate rise to follow: in contrast, non-selective drugs would block the peripheral effects of isoprenaline and the heart rate rise would be mainly through direct cardiac stimulation.

Recently we have shown that intravenous isoprenaline boluses produce a dose related increase in forearm blood flow (Arnold *et al.*, 1982). We have also demonstrated that isoprenaline boluses cause a fall in systemic blood pressure as well as a rise in heart rate, and that, after atropinisation, the fall in blood pressure is increased and the rise in heart rate is reduced, indicating that reflex withdrawal of cardiac vagal tone does occur (Arnold & McDevitt, 1983). The present study was designed to test the importance of this vagal reflex as an explanation for the different potencies of cardioselective and non-selective β-adrenoceptor antagonists when assessed by standardised isoprenaline sensitivity tests.

Methods

Approval for the study was obtained from the University Ethical Committee.

Six healthy non-smoking volunteers (three male,

three female; aged 19–23 years; weight 54.0–82.7 kg) were studied on two afternoons at least 7 days apart. After a light lunch containing no caffeine, an intra-arterial cannula (Abbocath 20G) was inserted in the radial artery under local anaesthesia and blood pressure continuously measured (Bell & Howell 4–422) and recorded (Devices MX4). An intravenous line (Butterfly 19G) was inserted into a major forearm vein in the same arm for the subsequent infusion of β-adrenoceptor blocking drug, and in the contralateral arm for the graded bolus injections of isoprenaline sulphate, which was freshly prepared in saline 0.9% with sodium metabisulphite 0.1% as preservative. This was injected into the sleeve of the fast running drip by the method of Cleaveland *et al.* (1972) and flushed with a total of 15 ml saline 0.9% (Buretrol i.v. administration set). Five points were obtained for construction of the dose-response curves. Heart rate was monitored from chest leads through an instantaneous ratemeter (Devices 4522) and recorder (Devices MX4) but changes in heart rate were measured from the shortest time between four consecutive R waves on an ECG rhythm strip (limb lead II; Minigraph Type 123, Cardiac Recorders Ltd). Control heart rate was recorded during 45 s preceding the isoprenaline injection, and the peak response during a further 45 s recording period which commenced 30 s after isoprenaline injection. Changes in respiration were measured by a transducer around the chest wall (Lectromed 4320).

Each afternoon, after 30 min supine rest, three dose-response curves were constructed for the changes in heart rate and blood pressure to isoprenaline boluses: (1) control, (2) with a β-adrenoceptor antagonist PRE-atropine sulphate (0.04 mg/kg i.v.), (3) with the β-adrenoceptor antagonist POST-atropine (Figure 1). Rapid and slow infusion rates for propranolol (19.09 $\mu g\ kg^{-1}\ min^{-1}$ and 1.07 $\mu g\ kg^{-1}\ min^{-1}$) and practolol (152.8 $\mu g\ kg^{-1}\ min^{-1}$ and 2.5 $\mu g\ kg^{-1}\ min^{-1}$) were calculated from the equations of Wagner (1974). These were estimated to produce plasma drug levels of 75 ng/ml for propranolol and 1.25 μg/ml for practolol, which would remain stable from the finish of the rapid infusion, which lasted 15 min. The pharmacokinetic data substituted in the equations were obtained from Shand (1974). Plasma drug levels were measured at the times indicated in Figure 1: (a) before commencement of β-antagonist infusion, (b) at 45 min immediately before construction of the PRE-atropine dose-response curves for isoprenaline, (c) immediately before construction of the POST-atropine dose-response curves, (d) on completion of the experiment. Propranolol was measured by gas-liquid chromatography with electron capture detection (Kinney, 1981) and practolol by high performance liquid chromatography.

The same six subjects were also studied on four further occasions at approximately weekly intervals. Following a light breakfast containing no caffeine, a 3 min control exercise step test (46 cm step, 32 steps/min) was performed. Blood pressure was measured (Critikon Exercise Monitor, Model 1165) during the last 30 s of exercise and heart rate was measured from the shortest five consecutive R-R intervals during the

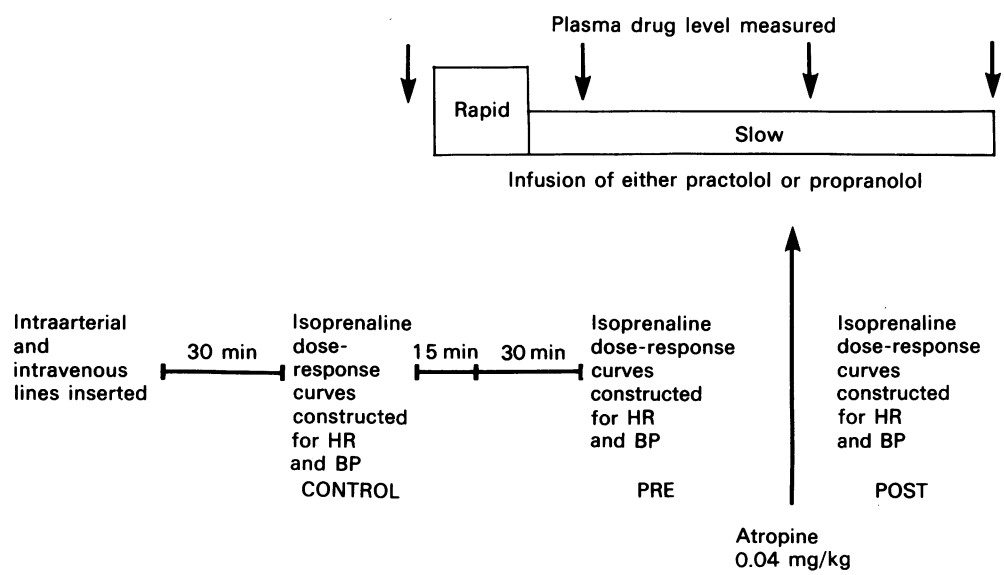

Figure 1 Plan of the experiment to demonstrate the timing of dose-response curve construction, β-adrenoceptor antagonist infusion, and plasma drug concentration measurements.

first 5 s at the end of exercise. In a single blind, randomised order, the previous infusion rates of propranolol and practolol, or a placebo infusion of saline 0.9%, were given intravenously and a second 3 min exercise step test performed at 60 min. On the fourth morning, the infusion of propranolol was given without prior exercise, but with the post-drug exercise test performed as before at 60 min. Plasma drug levels were measured immediately prior to the post-drug exercise test.

The results were compared statistically by analysis of co-variance and by Student's *t*-test for paired or unpaired data. Results are expressed as the mean ± s.e. mean.

Results

During the afternoon experiments, the plasma concentrations of propranolol and practolol did not vary significantly (Table 1), indicating that steady-state had been achieved. The overall mean propranolol concentration was 110.1 ± 3.4 ng/ml and the overall mean practolol concentration was 1.35 ± 0.08 μg/ml. During the morning exercise test, the plasma concentration of propranolol with prior exercise was 68.5 ± 5.4 ng/ml, but without prior exercise was 110.0 ± 8.3 ng/ml ($P < 0.001$). This latter concentration and the morning concentration of practolol (1.73 ± 0.10 μg/ml) were not significantly different from the corresponding sample (b) of the afternoon readings.

Heart rate and blood pressure changes with exercise

On the placebo infusion morning, the control exercise tachycardia was 186.7 ± 2.4 beats/min with a systolic pressure of 135.3 ± 8.4 mm Hg and a diastolic pressure of 66.5 ± 9.1 mm Hg. There was no significant difference between the control readings on the different mornings. The placebo infusion did not produce significant changes in either heart rate or blood pressure. Propranolol without prior exercise did not significantly alter exercise blood pressure but reduced the maximum tachycardia by 26.1 ± 2.7% ($P < 0.001$). On the morning with prior exercise, when the propranolol concentration was significantly reduced, the maximum tachycardia was reduced by 24.2 ± 1.9%, which was significantly different from control ($P < 0.001$) but not from propranolol without prior exercise. Practolol did not significantly alter exercise blood pressure but did significantly reduce the maximum tachycardia by 21.2 ± 1.9% ($P < 0.001$). This was not significantly different from the effects of propranolol.

Effects of propranolol, practolol and atropine on resting heart rate and blood pressure

Propranolol significantly reduced resting heart rate (59.3 ± 2.5 to 50.5 ± 1.6 beats/min; $P < 0.01$) and mean blood pressure (86.7 ± 3.5 to 79.6 ± 4.5 mm Hg; $P < 0.01$). Practolol had no significant effect on resting heart rate (60.2 ± 4.0 to 62.2 ± 3.3 beats/min) or mean blood pressure (82.9 ± 5.3 to 86.5 ± 4.4. mm Hg). Atropine significantly increased the propranolol resting heart rate to 105.8 ± 4.2 beats/min ($P < 0.01$), an increment of 51.3 ± 6.5 beats/min, and the practolol resting heart rate to 116.2 ± 4.3 beats/min ($P < 0.01$), an increment of 53.5 ± 4.8 beats/min. Atropine significantly increased the propranolol resting mean pressure from 82.8 ± 4.0 to 95.1 ± 5.1 mm Hg ($P < 0.01$) and the practolol resting mean pressure from 80.2 ± 3.4 to 93.0 ± 7.1 mm Hg ($P < 0.05$). After atropine, the new resting mean pressure for propranolol was not different from that for practolol.

Table 1 Plasma concentrations of propranolol and practolol during studies with isoprenaline and exercise. Results are shown as mean of six subjects ± s.e. mean

	Isoprenaline study	*Exercise study*	
		With prior exercise	*Without prior exercise*
Propranolol (ng/ml)	(a)† 0.0	0.0	0.0
	(b) 114.0 ± 4.6	68.5 ± 5.4*	110.0 ± 8.3*
	(c) 111.2 ± 6.0*		
	(d) 105.2 ± 7.3*		
Practolol (ng/ml)	(a) 0.0	0.0	
	(b) 1.54 ± 0.15	1.73 ± 0.10	
	(c) 1.33 ± 0.11		
	(d) 1.18 ± 0.15		

* $P < 0.01$ when compared to corresponding samples of isoprenaline study and study without prior exercise

† For sample times, see **Methods**

Time sequence of isoprenaline induced events (Table 2)

After an intravenous bolus injection of isoprenaline an increase in respiratory drive occurred at approximately 30 s followed by an increase in heart rate and blood pressure which was maximum at approximately 50 s. There was no significant difference between the control values on the two days. Propranolol caused the breathing change, heart rate and blood pressure maximums to occur significantly later, the most marked effect being seen with blood pressure (approximately 11 s). Practolol had no effect on breathing change or heart rate maximum but significantly shortened the time to blood pressure maximum by approximately 4 s. Atropine significantly shortened the time to breathing change and blood pressure maximum for both propranolol and practolol; it had no effect on the time to heart rate maximum for propranolol, but lengthened it by approximately 5 s for practolol.

Isoprenaline-induced heart rate changes

Dose-response curves were drawn for the increases in heart rate produced by isoprenaline and the results of one representative subject are shown in Figure 2. The slopes of the dose response curves are shown for all six subjects in Table 3. There was no significant difference between the control slopes on the two afternoons. After propranolol, the slope was significantly steeper ($P < 0.01$) but this was reduced significantly by atropine. After practolol, the slope tended to be shallower but this did not reach statistical significance. POST-atropine the slope was significantly steeper than either the control or practolol values.

From the individual regression equations, the dose of isoprenaline (I_{25}) required to increase heart rate by 25 beats/min was calculated (Table 4) and statistical comparisons were made with the log transformed data. There was no significant difference between the control values on the two afternoons. As propranolol shifted the dose response curves to the right it increased the I_{25} from 1.49 ± 0.44 to 65.10 ± 14.05 μg ($P < 0.01$; dose ratio 43.7), but POST-atropine no further significant change occurred (61.29 ± 13.46 μg; dose ratio 41.1). When substituted into the respective regression equations, the dose of isoprenaline which increased heart rate by 25 beats/min in the presence of propranolol, increased heart rate a similar amount, 25.9 ± 1.8 beats/min, POST-atropine. Practolol also shifted the dose-response curves to the right and increased the I_{25} from 1.39 ± 0.24 to 6.17 ± 1.46 μg ($P < 0.01$; dose ratio 4.4). POST-atropine there was a further shift of the dose-response curve to the right with an increase in I_{25} to 12.22 ± 2.74 μg ($P < 0.01$; dose ratio 8.8), though this remained significantly less than either the PRE- or POST-atropine

Table 2 Time in seconds following intravenous bolus isoprenaline injections to the change in breathing pattern and maximum change in heart rate and blood pressure. Results are shown as CONTROL, PRE- and POST-atropine (ATR) in the presence of propranolol and practolol. The number of observations is shown in parenthesis and the results are tabulated as the mean ± s.e. mean

	Propranolol			*Practolol*		
	CONTROL	*PRE-ATR*	*POST-ATR*	*CONTROL*	*PRE-ATR*	*POST-ATR*
Breathing change	29.4 ± 1.0 (25)	32.3 ± 1.0* (28)	24.2 ± 0.7† (30)	30.5 ± 0.9 (25)	29.3 ± 1.0 (25)	22.6 ± 0.6† (28)
Heart rate maximum	48.6 ± 1.2 (30)	56.3 ± 1.5** (30)	53.0 ± 1.8 (30)	52.0 ± 1.4 (30)	49.2 ± 1.1 (30)	54.3 ± 1.0† (30)
Blood pressure maximum	52.2 ± 1.3 (29)	63.0 ± 2.0** (26)	50.3 ± 1.9† (30)	51.4 ± 1.3 (27)	47.3 ± 1.2* (30)	41.3 ± 1.1† (30)

* $P < 0.05$, ** $P < 0.01$ when compared to CONTROL
† $P < 0.01$ when compared to PRE-atropine

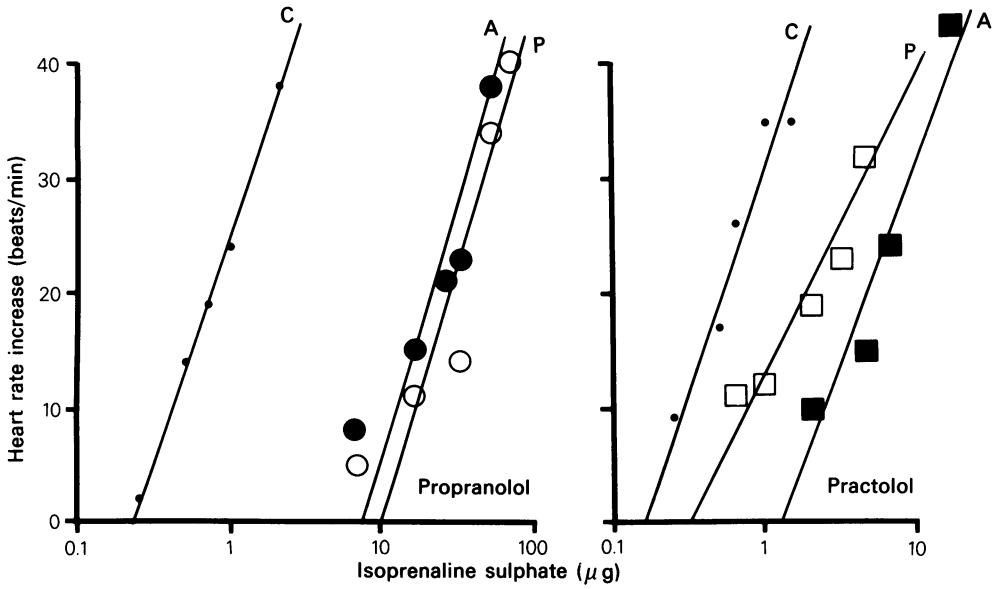

Figure 2 Dose-response curves of one representative subject (no. 1) of the increase in heart rate (beats/min) following graded intravenous bolus injections of isoprenaline sulphate (μg) in the presence of propranolol and practolol. Control C (●——●), PRE-atropine P (open symbols) and POST-atropine A (closed symbols) curves are shown.

values for propranolol ($P < 0.01$). The dose of isoprenaline which increased the heart rate by 25 beats/min in the presence of practolol, produced a significantly smaller rise in heart rate POST-atropine (11.8 ± 3.8 beats/min, $P < 0.05$).

Isoprenaline-induced blood pressure changes

Representative tracings from one subject are shown in Figure 3 and illustrate the different patterns of haemodynamic change with the fall in blood pressure being attenuated by propranolol but accentuated by practolol. Dose-response curves were drawn for the changes in diastolic, systolic and mean blood pressure produced by isoprenaline and the results from a representative subject are shown in Figure 4. The slopes of these dose-response curves are shown in Table 5. There was no significant difference between the control slopes on the two afternoons for either diastolic, systolic or mean blood pressure.

Diastolic pressure

Isoprenaline produced a dose-dependent fall in dia-

Table 3 Slopes (beats min^{-1} $ln\ \mu g^{-1}$) of the dose response curves for the increases in heart rate following intravenous isoprenaline. For each of six subjects the results are shown as CONTROL, PRE- and POST-atropine, in the presence of propranolol and practolol

Subject	*Propranolol*			*Practolol*		
	CONTROL	*PRE*	*POST*	*CONTROL*	*PRE*	*POST*
1	17.0	16.5	15.2	16.2	13.4	15.6
2	16.6	24.6	15.4	15.1	7.1	17.2
3	20.3	26.2	20.3	14.3	12.1	19.3
4	8.4	15.9	16.4	16.3	12.6	18.6
5	11.7	18.4	16.1	13.6	13.1	24.6
6	16.4	20.0	19.9	11.5	11.7	16.0
Mean	15.1	20.3*	17.2†	14.5	11.7	18.6*††
s.e. mean	1.7	1.7	0.9	0.7	0.9	1.3

* $P < 0.01$ when compared to CONTROL
† $P < 0.05$, †† $P < 0.01$ when compared to PRE-atropine

Table 4 Dose of isoprenaline (μg), I_{25}, required to increase heart rate by 25 beats/min for each of six subjects. The results are shown as CONTROL, PRE- and POST-atropine, in the presence of propranolol and practolol

Subject	*Propranolol*			*Practolol*		
	CONTROL	*PRE*	*POST*	*CONTROL*	*PRE*	*POST*
1	0.98	34.21	28.57	0.69	2.88	6.43
2	0.79	48.72	48.27	1.17	3.38	6.42
3	1.33	70.11	68.69	1.67	12.70	15.78
4	1.54	87.29	118.36	1.48	6.18	23.69
5	3.58	119.77	70.78	2.34	4.84	12.45
6	0.71	30.50	33.07	1.01	7.02	8.57
Mean	1.49	65.10*	61.29*	1.39	6.17*	12.22*†
s.e. mean	0.44	14.05	13.46	0.24	1.46	2.74
Dose ratio		43.7	41.1	4.4	8.8	

* $P < 0.01$ when compared to CONTROL
† $P < 0.01$ when compared to PRE-atropine, practolol and propranolol

stolic pressure with a parallel shift to the right by both propranolol and practolol. To obtain dose ratios for the degree of shift, the curves were compared at the dose of isoprenaline which decreased diastolic pressure by 10 mm Hg. For propranolol, this could only be calculated for five subjects as one subject (no. 4) showed a flat dose-response curve, with a fall in diastolic pressure of less than 10 mm Hg even with the largest PRE-atropine dose of isoprenaline. From the individual regression equations, the isoprenaline dose required to decrease diastolic pressure 10 mm Hg was significantly increased by propranolol from 0.93 ± 0.21 to 90.32 ± 12.1 μg ($P < 0.01$; dose ratio 97.5). Practolol produced a much smaller non-significant increase from 1.81 ± 1.01 to 2.43 ± 1.03 μg of isoprenaline (dose ratio 1.3).

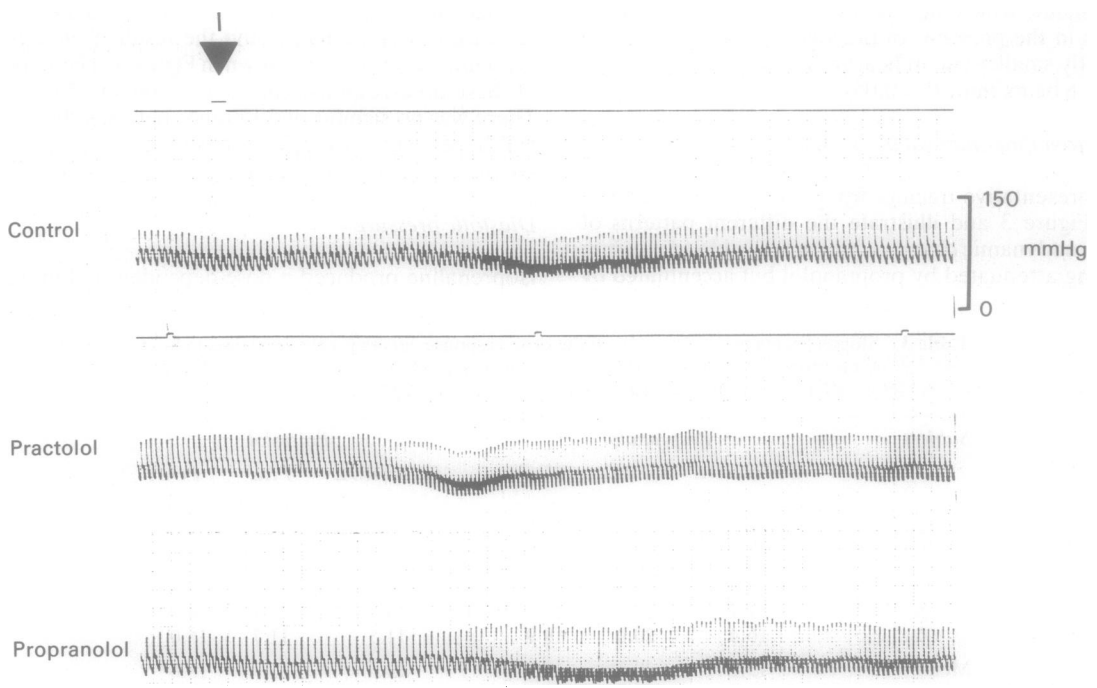

Figure 3 Intra-arterial blood pressure tracings from the representative subject (no. 1) of the time course of changes in blood pressure following an intravenous bolus (I) of the isoprenaline dose which most closely produced a heart rate increase of 25 beats/min.

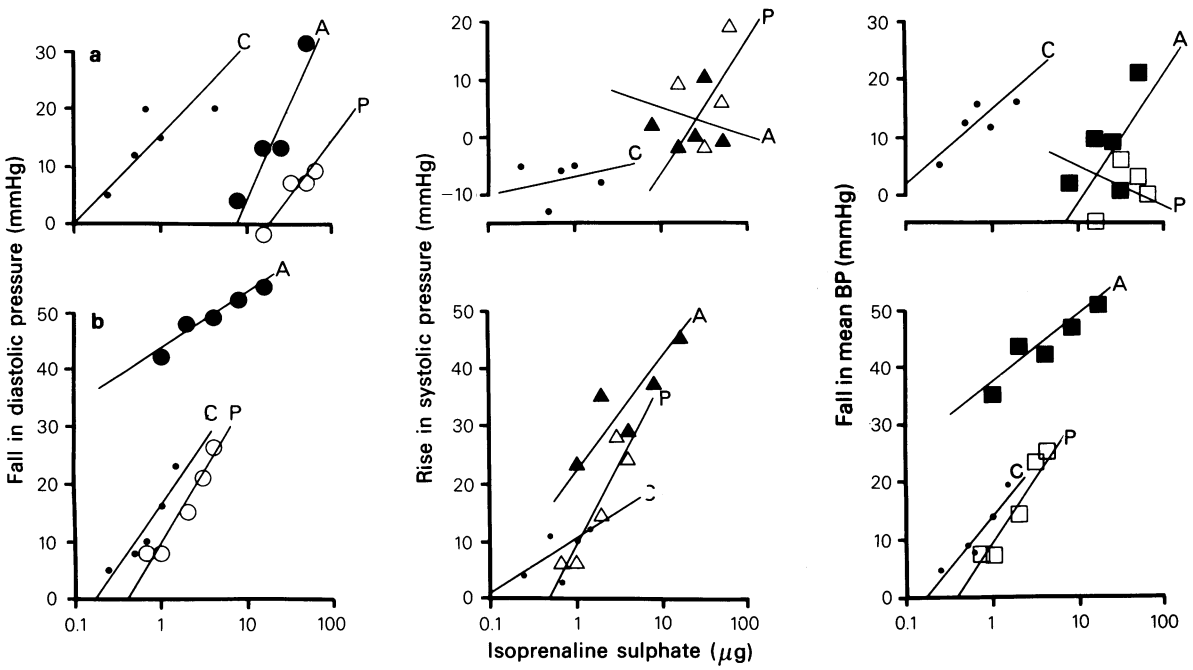

Figure 4 Dose-response curves from one representative subject (no. 1) for the isoprenaline induced changes in diastolic, systolic and mean blood pressure in the presence of a) propranolol and b) practolol. Control C (●——●), PRE-atropine P (open symbols) and POST-atropine A (closed symbols) curves are shown.

At the dose of isoprenaline required to increase heart rate by 25 beats/min, the control fall in diastolic pressure, 12–14 mm Hg, was the same on both afternoons (Table 6). With propranolol, at the same heart rate rise, the fall in diastolic pressure was significantly less (5.6 ± 1.8 mm Hg; $P < 0.05$). POST-atropine, the dose-response curve was steeper ($P < 0.05$) and shifted to the left, so the PRE-atropine I_{25} produced a significantly greater fall (26.5 ± 5.0 mm Hg; $P < 0.01$). With practolol, there was a significantly greater PRE-atropine fall in diastolic pressure (20.7 ± 2.9 mm Hg; $P < 0.05$) than control. POST-atropine the dose-response curve tended to be shallower and was shifted to the left, so the PRE-atropine I_{25} caused a further significant fall in diastolic pressure (36.3 ± 4.8 mm Hg; $P < 0.01$).

Systolic pressure

The isoprenaline-induced control changes in systolic pressure tended to show some individual variation. In some subjects the response to increasing doses of isoprenaline was a fall in systolic pressure, in others it was a small rise. The changes were therefore analysed and compared at the dose of isoprenaline (I_{25}) which increased heart rate by 25 beats/min (Table 7). There was no significant difference in the two afternoons between the control responses (falls of 3.2 ± 2.3 and 3.3 ± 3.7 mm Hg).

Table 5 Slopes (mm Hg ln μg^{-1}) of the dose-response curves for the isoprenaline induced falls in diastolic, systolic and mean blood pressure (as CONTROL, PRE- and POST-atropine) in the presence of propranolol and practolol. Mean of six subjects ± s.e. mean

	Propranolol			*Practolol*		
	CONTROL	*PRE*	*POST*	*CONTROL*	*PRE*	*POST*
Diastolic	9.9 ± 2.4	10.8 ± 3.2	16.4 ± 2.8*†	9.0 ± 2.1	9.4 ± 0.7	5.6 ± 1.3
Systolic	−2.4 ± 3.2	−11.6 ± 5.0*	3.8 ± 2.3††	3.5 ± 3.4	7.9 ± 3.4	12.3 ± 3.5*
Mean	4.6 ± 1.3	1.1 ± 2.6	11.1 ± 2.2*††	8.0 ± 2.7	9.2 ± 1.3	8.3 ± 1.9

* $P < 0.01$ when compared to corresponding CONTROL
† $P < 0.05$, †† $P < 0.01$ when compared to corresponding PRE-atropine

Table 6 Fall in diastolic blood pressure (mm Hg) for each of six subjects, in the presence of propranolol and practolol. CONTROL and PRE-atropine values are at the respective dose of isoprenaline (I_{25}) which increased heart rate 25 beats/min. POST-atropine values are at the PRE-atropine I_{25} isoprenaline dose

Subject	*Propranolol*			*Practolol*		
	CONTROL	*PRE*	*POST (at pre I_{25})*	*CONTROL*	*PRE*	*POST (at pre I_{25})*
1	16.5	6.9	18.2	11.3	20.9	47.7
2	12.0	4.2	38.4	14.7	21.7	47.9
3	9.4	4.3	37.4	18.8	30.9	44.8
4	7.0	7.0	11.6	13.9	17.9	26.6
5	22.7	12.4	36.6	21.9	23.1	29.1
6	8.1	+1.2	16.8	5.3	9.5	21.8
Mean	12.6	5.6*	26.5**†	14.3	20.7*	36.3**†
s.e. mean	2.5	1.8	5.0	2.4	2.9	4.8

* $P < 0.05$, ** $P < 0.01$ when compared to CONTROL
† $P < 0.01$ when compared to PRE-atropine

In the presence of propranolol, the PRE-atropine I_{25} caused a significant rise in systolic pressure (+16.2 ± 3.6 mm Hg; $P < 0.01$ compared to control). The same dose of isoprenaline produced a significantly smaller rise POST-atropine (+2.9 ± 2.1 mm Hg; $P < 0.01$). With practolol, the PRE-atropine I_{25} caused a significantly greater fall in systolic pressure (16.6 ± 4.9 mm Hg; $P < 0.01$) than control, and the same dose caused a significant further fall POST-atropine (35.5 ± 5.4 mm Hg; $P < 0.01$).

Mean pressure

The changes in mean pressure were also analysed at the I_{25} dose of isoprenaline (Table 8). There was no significant difference on the two afternoons between the control responses (falls of 9.8 ± 1.9 and 11.0 ± 2.2 mm Hg). With propranolol, the PRE-atropine I_{25} caused a small rise in mean pressure (+ 2.3 ± 1.3 mm Hg; $P < 0.01$ when compared to control). The same dose of isoprenaline produced a significant fall POST-atropine (15.5 ± 2.9 mm Hg; $P < 0.01$). With practolol, the PRE-atropine I_{25} caused a significantly greater fall than control (19.7 ± 2.9 mm Hg; $P < 0.01$) and the same dose caused a significant further fall POST-atropine (35.9 ± 44.0 mm Hg; $P < 0.01$).

Discussion

The results of this present study confirm that doses of cardioselective and non-selective β-adrenoceptor antagonists which have comparable effects on exercise tachycardia may show quite different potency

Table 7 Fall in systolic blood pressure (mm Hg), for each of six subjects, in the presence of propranolol and practolol. CONTROL and PRE-atropine values are at the respective doses of isoprenaline (I_{25}) which increased heart rate 25 beats/min. POST-atropine values are at the PRE-atropine I_{25} isoprenaline dose

Subject	*Propranolol*			*Practolol*		
	CONTROL	*PRE*	*POST (at pre I_{25})*	*CONTROL*	*PRE*	*POST (at pre I_{25})*
1	7.4	+5.0	+2.2	8.1	22.0	31.6
2	+2.7	+20.5	+2.3	+3.7	3.2	28.7
3	+4.4	+29.7	+11.0	2.5	23.7	50.0
4	9.0	+18.2	4.3	17.5	28.9	47.2
5	6.3	+15.3	+0.6	3.5	21.9	31.8
6	3.5	+8.7	+5.7	+8.3	+0.4	13.6
Mean	3.2	+16.2**	+2.9†	3.3	16.6**	35.5**†
s.e. mean	2.3	3.6	2.1	3.7	4.9	5.4

** $P < 0.01$ when compared to CONTROL
† $P < 0.01$ when compared to PRE-atropine

Table 8 Fall in mean blood pressure (mm Hg), for each of six subjects, in the presence of propranolol and practolol. CONTROL and PRE-atropine values are at the respective doses of isoprenaline (I_{25}) which increased heart rate 25 beats/min. POST-atropine values are at the PRE-atropine I_{25} isoprenaline dose. Mean pressure was calculated as diastolic pressure plus one-third of the pulse pressure.

Subject	*Propranolol*			*Practolol*		
	CONTROL	*PRE*	*POST (at pre I_{25})*	*CONTROL*	*PRE*	*POST (at pre I_{25})*
1	13.6	0.8	11.4	12.4	21.2	42.3
2	7.9	+4.1	20.1	8.9	18.8	45.0
3	4.4	+6.3	20.3	13.4	27.6	46.6
4	9.3	+3.3	9.2	15.1	21.6	33.3
5	17.1	2.1	24.4	15.1	22.7	29.6
6	6.6	+2.8	7.6	1.2	6.3	18.6
Mean	9.8	+2.3**	15.5*†	11.0	19.7**	35.9**†
s.e. mean	1.9	1.3	2.9	2.2	2.9	4.4

* $P < 0.05$, ** $P < 0.01$ when compared to CONTROL
† $P < 0.01$ when compared to PRE-atropine

when tested against an isoprenaline tachycardia. Thus the infusion rates of propranolol and practolol used produced mean reductions in exercise tachycardia of 26 and 21% respectively which were not significantly different. In contrast, the same infusion rates, tested by standardised isoprenaline bolus injections, resulted in mean dose-ratios of 43.7 and 4.4 for propranolol and practolol respectively, or an apparent difference in potency of approximately ten-fold between the two compounds.

After atropinisation, the comparable isoprenaline mean dose-ratios were 41.1 for propranolol and 8.8 for practolol, with the difference in potency between the two drugs approximately halved. These results would suggest, firstly, that a vagal reflex as a component of isoprenaline-induced tachycardia (Arnold & McDevitt, 1983) continues to operate in the presence of cardio-selective β-adrenoceptor antagonists but not with non-selective drugs, and secondly, that this explains part of the observed differences in potency between these two types of compound on isoprenaline and exercise testing. In fact, since the reflex operates both in the drug-free state and with cardio-selective antagonists, it is the absence of the reflex with non-selective drugs which is the variant and which results in an overestimate of the potency of this type of compound. However, it is clear from these results that other, currently unidentified, factors must also contribute to the observed potency differences on isoprenaline testing, since, even after the vagal reflex was abolished by atropinisation, the dose-ratios for propranolol and practolol continued to show a 4–5 fold difference. One possible factor might be the presence of cardiac β_2-adrenoceptors. These have been demonstrated in animals (Ablad *et al.*, 1974), but, at present, proof is lacking of their existence in man.

In the control curves, the isoprenaline-induced changes in diastolic, systolic and mean blood pressure are similar to those reported previously (Arnold & McDevitt, 1983). Propranolol blocked both β_1-receptors, as evidenced by the reduction in exercise tachycardia, and β_2-receptors, as evidenced by the shift to the right of the dose-response curve for the isoprenaline produced fall in diastolic pressure. The dose-ratio for propranolol's effect on diastolic pressure (97.5), was more than double its effect on heart rate (43.7). Thus, following isoprenaline, propranolol reduced the fall in diastolic pressure and allowed a significant rise in systolic and mean pressures. Practolol, however, while blocking β_1-receptors to the same extent as propranolol (exercise tachycardia), did not block β_2-receptors as there was no significant shift to the right of the isoprenaline dose-response curve for diastolic pressure. Hence, following isoprenaline, practolol allowed large falls in diastolic, systolic and mean pressures.

The effects of atropine on the isoprenaline-induced cardiovascular changes were different with the two β-adrenoceptor antagonists studied. The greater fall in blood pressure with practolol plus atropine could be predicted from the presence of a vagal reflex, but, as this was not important for propranolol, the fall in blood pressure with propranolol plus atropine was not expected. It suggests that atropine allows a greater fall in blood pressure with isoprenaline by some further mechanism apart from the contribution of a reflex tachycardia. With practolol the fall in diastolic pressure was increased by approximately 16 mm Hg with atropine. However, as this was

associated with absolute diastolic pressures of around 20 mm Hg it is feasible that greater falls were not possible and this is supported by the finding that the slope of the diastolic dose-response curve was significantly flatter post-practolol plus atropine.

Several other findings require comment. Firstly, the heart rate dose-response curves were parallel on the two control readings, though with propranolol the slope was significantly steeper and with practolol it tended to be shallower but did not reach statistical significance. However, the laws of competitive blockade are not strictly applicable as we have demonstrated that the heart rate response depends on more variables than pure antagonism at β_1-adrenoceptors. Secondly, propranolol tended to cause the changes in breathing, heart rate and blood pressure to occur later, possibly either as a result of a lengthened circulation time due to the slower resting heart rate, or because of its β_2-adrenoceptor blockade. However, with respect to the former, as normal venous to systemic circulation time is approximately 15 s (Ganong, 1981) it is unlikely that the relatively small slowing of resting heart rate alone by propranolol would have delayed the blood pressure maximum by the observed 11 s. Though propranolol lengthened the time to maximum blood pressure change, practolol shortened it, illustrating their different haemodynamic effects. Thirdly, with practolol plus atropine, the heart rate and blood pressure responses became disassociated by approximately 13 s. This tends to support the concept that with practolol alone, the heart rate response may be partly dependent on and modified by changes in blood pressure. Finally, on the exercise tests, though propranolol was given by identical infusion rates, the plasma concentration depended on the presence or otherwise of prior exercise. As exercise decreases liver blood flow, it might have been expected that the plasma levels would have risen rather than decreased (Powis & Snow, 1978) and therefore the altered plasma levels may reflect altered disposition of the drug rather than clearance.

In summary, the present results demonstrate that the shift of the isoprenaline bolus heart rate dose-response curve to the right by practolol is limited because the unblocked β_2-receptors allow a fall in blood pressure and a contribution to the heart rate rise from a withdrawal of cardiac vagal tone. However, this contribution does not fully explain the remaining difference between practolol and propranolol. Hence the shift of an isoprenaline bolus heart rate dose-response curve to the right does not reflect blockade of solely β_1-receptors.

References

ABLAD, B., CARLSSON, B., CARLSSON, E., DAHLOF, C., EK, L. & HULTBERG, E. (1974). Cardiac effects of β-adrenergic receptor antagonists. *Adv. Cardiol.*, **12**, 290–302.

ARNOLD, J.M.O., ALLEN, J.A., SHANKS, R.G. & McDEVITT, D.G. (1983). Changes in heart rate and forearm blood flow following intravenous boluses of isoprenaline in the presence of practolol and propranolol. *Br. J. clin. Pharmac.*, **15**, 37–40.

ARNOLD, J.M.O. & McDEVITT, D.G. (1983). Contribution of the vagus to the haemodynamic responses following intravenous boluses of isoprenaline. *Br. J. clin. Pharmac.*, **15**, 423–429.

BRICK, I., HUTCHINSON, K.J., McDEVITT, D.G., RODDIE, I.C. & SHANKS, R.G. (1968). Comparison of the effects of ICI 50172 and propranolol on the cardiovascular response to adrenaline, isoprenaline and exercise. *Br. J. Pharmac.*, **34**, 127–140.

CLEAVELAND, C.R., RANGNO, R.E. & SHAND, D.G. (1972). A standardised isoproterenol sensitivity test. *Arch. intern. Med.*, **130**, 47–52.

DE PLAEN, J.F., AMERY, A. & REYBROUCK, T. (1976). Comparative potency of atenolol and propranolol as beta-adrenergic blocking agents in man. *Eur. J. clin. Pharmac.*, **10**, 297–303.

DUNLOP, D. & SHANKS, R.G. (1968). Selective blockade of adrenoceptor beta-receptors in the heart. *Br. J. Pharmac. Chemother.*, **32**, 201–218.

GANONG, W.F. (1981). *Review of Medical Physiology*, Ch. 30, p. 456. Los Altos, California: Lange Medical Publications.

KINNEY, C.D. (1981). Determination of metoprolol in plasma and urine by gas-liquid chromatography with electron capture detection. *J. Chromatogr.*, **225**, 213–218.

PERUCCA, E., PICKLES, H. & RICHENS, A. (1981). Effect of atenolol, metoprolol and propranolol on isoproterenol induced tremor and tachycardia in normal subjects. *Clin. Pharmac. Ther.*, **29**, 425–433.

POWIS, G. & SNOW, D.H. (1978). The effect of exercise and adrenaline infusion upon the blood levels of propranolol and antipyrine in the horse. *J. Pharmac. exp. Ther.*, **205**, 725–731.

SHAND, D.G. (1974). Pharmacokinetic properties of the β-adrenergic receptor blocking drugs. *Drugs*, **7**, 39–47.

WAGNER, J.G. (1974). A safe method for rapidly achieving plasma concentration plateaus. *Clin. Pharmac. Ther.*, **16**, 691–700.

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